IRIS PCB Assessment Team Meeting

Monday, February 13, 2017 **11:00 am – 12:00 pm**	**Location:** RTP-B230-Max20-NCEA/RTP-Bldg-B **Adobe Connect:** [HYPERLINK Ex. 6 Personal Privacy (PP) Call-in number: Ex. 6 Personal Privacy (PP) Conference code	**Facilitator:** Geniece Lehmann

Meeting objectives:

- Summarize status of ongoing tasks
- Review and update of procedures we will follow to develop mode of action analyses
- Xabier will present ongoing work to categorize MOA literature for male reproductive effects according to key characteristics of male reproductive toxicants
- Preliminary discussions of mechanistic events and pathways connecting PCB exposure with health outcomes

Attendees:

Required	Required
☐ Xabier Arzuaga	☐ Alex Sergeev
☐ Michael Bloom	☐ Michele Taylor
☐ Dave Burch	☐ Michal Toborek
☐ Laura Carlson	☐ Joanne Trgovcich
☐ Pam Factor-Litvak	☐ Mike Wright
☐ Todd Jusko	☐ Erin Yost
☐ Aileen Keating	
☐ Pamela Lein	**Optional**
☐ Jenny Li	☐ Natalie Blanton
☐ Danelle Lobdell	☐ Allen Davis
☐ April Luke	☐ Michael Dzierlenga
☐ John Meeker	☐ Anna Engstrom
☐ Anu Mudipalli	☐ Jeff Gift
☐ Larissa Pardo	☐ Allison Killius
☐ Amanda Persad	☐ Revathi Muralidharan
☐ Larry Robertson	☐ Paul Schlosser
☐ Marian Rutigliano	☐ John Stanek
☐ Sharon Sagiv	☐ Jim Walker
☐ MaryJane Selgrade	

Previous action items:

- ICF delivered the final lists of hazard id studies to add to literature inventories; EPA is reviewing prior to distribution to section authors
- ICF delivered the ADME literature search & screen report; will be complete after the addition of a few more references

Agenda items:

TASKS IN PROGRESS

- MOA literature search & screen - underway
- What is EPA working on?
  - Reviewing final lists of hazard id studies prior to distribution to section authors

- Reviewing hazard id literature inventories

	Human studies	Animal studies		Human studies	Animal studies
Cardiovascular effects	X	X	**Metabolic disease**	X	X
Dermal & ocular effects	X	X	**Neurological effects**	X	
Endocrine effects	X		**Renal effects**	X	X
Gastrointestinal effects	X		**Male reproductive effects**		
Hematological effects	X	X	**Female reproductive effects**	X	X
Hepatic effects	X		**Developmental effects**	X	
Immunological effects		X			

  - Developing criteria to identifying key health effect categories and endpoints for further evaluation
  - Developing a framework to support study quality evaluation

MOA ANALYSIS (procedures):

- Identify mechanistic events and pathways connecting PCB exposure with health outcomes
  - Supporting information will come from
    - hazard identification literature inventories
    - MOA-specific literature search and screen currently underway by ICF
    - pathway-targeted literature searches (as necessary)
- Team toxicologists will organize MOA studies into a first-tier literature inventory with information including
  - Citation information
  - Exclusion justifications (for any studies determined not to be relevant for MOA analysis)
  - Test compound (mixture or congener tested)
  - Route of exposure (*in vivo* vs. *in vitro*)
  - Species/strain
  - Cell type/tissue/body fluid
  - Mechanistic endpoints
  - MOA "categories" (Xabier will provide an illustration of this type of categorization)
- Based on the first-tier inventory, team toxicologists will decide
  - If there are sufficient data to conduct a MOA analysis for their health effect category
    - For some health effect categories, it may not be necessary to develop a first-tier inventory to come to the conclusion that a MOA analysis is not warranted
    - Criteria used to determine which health effect categories require a MOA analysis:
      - Strength of evidence connecting PCB exposure to health effects; MOA analysis will not be necessary for health effect categories with inadequate information to assess toxic potential of PCBs or with evidence of no impact of PCB exposure
      - Availability of evidence to support a MOA hypothesis; evidence should be available to support an impact of PCBs on more than one key event in a mechanistic pathway connecting PCB exposure with a health effect
  - If there is a need for an additional (targeted) literature search to identify more information for one or more potential mechanistic pathways
    - Targeted literature searches should be developed for MOA-related events associated with any MOA hypothesis that will be analyzed in the assessment

    - Targeted searches will use keywords and search strings developed by PCB team toxicologists, but will be conducted and documented by ICF
    - At a future PCB team meeting, we will meet with information specialists from HERO and ICF to discuss the identification of keywords and the development of search strings for targeted MOA literature searches
    - If one or more targeted literature searches are conducted, team toxicologists will add the results of these searches to the first-tier literature inventory
- Team toxicologists will submit first-tier literature inventories to ICF with instructions for extraction of additional study details as necessary to support MOA analysis
- MOA evidence will be evaluated and presented by team toxicologists according to guidance provided in the IRIS Handbook (Section 9) and by the IRIS Toxicity Pathway Workgroup (details to be provided at a later date).

MOA ANALYSIS (Methods of categorizing MOA literature – Xabier)

MOA ANALYSIS (Group discussion of MOA information collected so far):

- PCB team toxicologists should look for opportunities to collaborate with other section authors.
    - MOAs may overlap across health effect categories, and this may provide an opportunity for authors to work together to develop a single MOA analysis that addresses multiple health effects (e.g., AhR pathway).
    - Also, studies in some health effect categories may provide MOA information for another health effect category (e.g., thyroid hormone disruption may contribute to neurodevelopmental or repro/developmental endpoints).
- PCB team epidemiologists should use their literature inventories to identify studies with information that may contribute to an understanding of MOA and share these studies with the relevant animal toxicology section authors.
- Michael Bloom (endocrine effects – human studies)
    - Associations have been measured between hydrophilic PCB metabolites in human serum or plasma and thyroid hormones, including hydroxylated PCBs (OH-PCBs) and methylsulfonated PCBs (MeSO2-PCBs).
        - HERO ID #'s: 1442711, 199563, 199055, 2924674, 199865, 2149421, 2150479, 2149477, 758053, and 2153149
        - Potential role of PCB metabolism in effects on thyroid hormones – is there corroborating evidence from animal or in vitro studies?
    - Some human studies have operationalized PCBs based on purported biologic activity, including estrogenic effects, anti-estrogenic effects, dioxin-like effects/TEQs, non-dioxin-like effects, phenobarbital-CYP1A-CPY2B-inducing effects, immunotoxic effects, UDP-GT-CYP1A-EROD-CYP2B-PROD effects, thyroid binding protein effects, ortho-PCBs, and non-ortho-PCBs.
        - HERO ID #'s:1510325, 2155465, 2919780, 594408, 199678, 197881, 198443, 644435, 197206, 199675, 198734, 2154433, 2919671, 2920622, 2188758, 2153087, and 198449
        - What is the strength of evidence from animal or in vitro studies to support these groupings?
    - Human studies have measured auto-immune thyroid disease biomarkers, including anti-thyroid peroxidase antibody (TPOab), thyroid receptor antibody (TRab), and TSH receptor antibody (TSHRab).
        - HERO ID #'s: 2160246, 2920316, 1510293, 1510329, 625019, 2177697, and 2154690
        - Possible connection between PCB effects on the immune system and effects on thyroid hormones? Corroborating evidence from animal or in vitro studies?
    - Human studies have measured serum thyroid hormone carrier proteins, including thyroid binding globulin (TBG) and transthyretin (TTR).
        - HERO ID #'s: 198734, 2149421, 2177697, 2150479, 2188758, and 2149477
        - How do the results of these studies compare with similar studies in animals and with what is known from in vitro studies?

Project risks, issues and concerns*:*

Decisions/Action items:

WHO	TASK	DUE
Team toxicologists and epidemiologists	Draft inventories needed for sections with no "X" in the chart above.	**ASAP**
Geniece	Schedule team meeting with information specialists from HERO and ICF to discuss the identification of keywords and the development of search strings for targeted MOA literature searches	When first-tier MOA literature inventories are nearing completion

Parking lot review:

Items identified during the meeting that are not directly relevant to the discussion at hand will be "parked" to avoid derailing the discussion. These items will be reviewed and resolved offline or at a future meeting.